Working Safely with H5N1 Viruses

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ABSTRACT **Research on H5N1 influenza viruses has received much attention recently due to the possible dangers associated with newly developed avian H5N1 viruses that were derived from highly pathogenic avian viruses and are now transmissible among ferrets via respiratory droplets. An appropriate discussion, based on scientific facts about the risks that such viruses pose and on the biocontainment facilities and practices necessary for working safely with these viruses, is needed. Selecting the right level of biocontainment is critical for minimizing the risks associated with H5N1 research while simultaneously allowing an appropriately fast pace of discovery. Rational countermeasures for preventing the spread of influenza can be developed only by gaining a thorough knowledge of the molecular mechanisms at work in host specificity and transmission.**

Influenza A viruses continue to pose a major concern for animal and human health. These viruses infect a variety of species, including aquatic birds, poultry, pigs, horses, dogs, and humans, causing significant morbidity and mortality. In the case of human influenza viruses, in addition to the burden of yearly epidemics, there is the ever-present threat of an influenza pandemic. Pandemics occur when a novel strain of influenza virus of animal origin evolves the ability to infect and efficiently transmit among humans. While some influenza pandemics, like the 1918 H1N1 pandemic that killed more than 40 million people worldwide, have had devastating consequences, others, including the H1N1 pandemic in 2009, which resulted in an estimated 18,000 deaths, have been considerably milder. Unfortunately, the emergence of new human pandemic viruses, as well as the subtype and virulence of the causative viruses, is still unpredictable. Although there are vaccines available for certain influenza viruses, they are strain specific, and the generation and general distribution of a new influenza virus vaccine take more time than the spread of a new virus, severely limiting the impact of vaccines in the first wave of a pandemic. Influenza antiviral drugs are of broader specificity, but resistance to those drugs and problems with availability limit their use.

In order to mitigate the possible impact of an influenza pandemic, we need more research and development in the generation of improved vaccines and antivirals with broad cross-reactivity against multiple influenza viruses. In addition, by investigating the factors responsible for the generation of human pandemic viruses, we can better recognize the risks that animal influenza virus strains pose to humans and build eradication campaigns to target specific viral strains circulating in animals. Critical to this issue is the question of what makes an influenza virus transmissible in humans and animals. We know very little about this question. A better understanding of influenza transmission will lead to the development of countermeasures for viral transmission that can enhance our pandemic preparedness plans.

Ferrets and guinea pigs are often used as animal models of influenza virus transmission. Several mutations and changes associated with increased airborne transmission of avian influenza viruses in ferrets have been identified in recent years (1–3). However, previous attempts to identify adaptive changes in highly pathogenic avian H5N1 viruses associated with transmission have failed, supporting the possibility that H5N1 viruses might be structurally unfit for mammalian transmission (4). More recently, two independent laboratories lead by Ron Fouchier and Yoshihiro Kawaoka have ruled out this hypothesis and identified specific mutations that allow the H5N1 virus to accomplish airborne transmission in ferrets (unpublished observations). While this provides important information on the adaptability of H5N1 viruses, more research needs to be conducted to understand the possibility that avian H5N1 could evolve to become transmissible in humans, to predict its pathogenesis in humans, and to find the molecular mechanisms responsible for host specificity in influenza virus transmission.

While research on influenza virus transmission is critical for finding ways to better tackle this pathogen, it is important to conduct such research using appropriate biocontainment and biosafety conditions to minimize possible risks of virus release to the environment. Risk assessment is a crucial tool in selecting biocontainment levels for research on potentially dangerous pathogens. According to the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) manual (5), the definitive reference book for biosafety issues, biological risk associated with pathogen research is determined by three elements: the activities that can result in human exposure to the pathogen, the probability that such exposure would cause an infection, and the consequences of such an infection. Although ferret-adapted H5N1 viruses probably have attenuated infectivity and pathogenesis for humans, to minimize all possible risks one should use biocontainment facilities and practices that prevent human exposure. Preventing the escape of viruses from the laboratory can be achieved by housing research activities in a facility equipped with interlocked rooms with negative pressure and high-efficiency particulate air (HEPA) filtered air circulation and using the appropriate decontamination and/or sterilization practices for material leaving the facility. Since human infection with influenza viruses occurs via the respiratory route, infection of laboratory personnel can be prevented by the use of powered air-purifying respirators. These practices correspond to enhanced biosafety level 3 (BSL3), as described in the

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BMBL manual. The effects of accidental exposure to the virus in an enhanced BSL3 facility can be minimized by vaccinating personnel with an H5N1 vaccine and through the use of antiviral drugs.

Increased biocontainment, or BSL4, is generally restricted to dangerous pathogens for which neither therapeutics nor vaccines are available. H5N1 viruses, on the other hand, are sensitive to the antivirals zanamivir and oseltamivir, and infection with the virus is preventable by vaccination with the H5N1 inactivated vaccine.

Influenza virus research is important for the development of novel intervention strategies for preventing and mitigating influenza epidemics and pandemics. As scientists, we have the responsibility to avoid the undue restrictions of the highest level of biocontainment if enhanced BSL3 facilities can provide the appropriate biosafety. The use of BSL4 containment would not decrease the risk of virus release any more than enhanced BSL3 containment, but it would result in an unnecessary burden that would restrict research on H5N1 influenza transmission to a few facilities and considerably decrease the speed of research on this important pathogen.

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